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**PRO-INFLAMMATORY DIETARY PATTERN
IS ASSOCIATED WITH FRACTURES IN WOMEN:
AN EIGHT YEAR LONGITUDINAL COHORT STUDY**

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ABSTRACT

Purpose: Inflammation is key risk factor for many adverse outcomes in older people. Whilst diet is a potential source of inflammation, little is known about the impact of inflammatory diet on fractures. Thus, we investigated whether higher Dietary Inflammatory Index (DII)TM scores are associated with fractures in a cohort of North American people.

Methods: This longitudinal with a follow-up of 8 years included 3,648 participants (1,577 Males and 2,071 Females; mean age: 60.6 years) with/at risk of knee osteoarthritis participating to the Osteoarthritis Initiative. DII scores were calculated using the validated Block Brief 2000 Food-Frequency Questionnaire, categorized into sex-specific quintiles. Information on fractures was obtained through self-reported history of fractures at hip, spine and forearm. The relationship between baseline DII score and incident fracture was assessed through a Cox's regression analysis, adjusted for potential baseline confounders, and reported as hazard ratios (HRs).

Results: During 8 years of follow-up, 560 individuals developed fractures (=15.4%). Adjusting for 10 potential confounders, women in the highest DII score quintile (i.e. most proinflammatory diet) had a significantly higher risk for fractures (HR: 1.46; 95% CI: 1.02-2.11) compared to women in the lowest quintile. An increase in one standard deviation of DII scores significantly predicted fracture onset in women (adjusted HR=1.14; 95%CI: 1.02-1.27). The association between DII score and fractures was not significant among men or in the sample as whole.

Conclusion: Pro-inflammatory diet is associated with a higher incidence of fractures in women but not men.

Keywords: aged; dietary inflammatory index; osteoporosis; fracture; inflammation.

MINI-ABSTRACT

In this study, during 8 years of follow-up, we reported that higher dietary inflammatory index values were associated with a higher risk of incident fractures in women, but not in men, also after adjusting for potential confounders.

INTRODUCTION

Worldwide, osteoporosis is the leading risk factor for over 8 million fractures annually, equating to an osteoporotic fracture every 3 seconds.[1] Osteoporosis and fractures are associated with several negative outcomes, such as increased risk of cardiovascular disease[2], hospitalization[3], poor quality of life[4], increased healthcare costs[4] and premature mortality.[4] Thus, elucidating the risk factors for osteoporosis and fractures is a public health priority, and key public health bodies (such as the World Health Organization) have developed strategies to prevent and manage poor bone health and fractures.[5]

Several factors are recognized as important for fractures. Physical inactivity and a sedentary lifestyle[6] are important factors for developing fragility fractures, as well as female gender[7], heavy smoking[8], alcohol drinking[9], low weight[10], psychiatric disorders (such as anorexia nervosa[11]) and the use of some medications.[12, 13]

The interest in inflammation as a potential risk factor is increasing. It is established that markers of inflammation linearly increase with age (a phenomenon commonly called “inflammaging”).[14] Several observational longitudinal studies examined the potential association between serum inflammatory markers and osteoporotic fractures, finding that higher inflammatory levels are associated with a higher risk of fractures.[15-20] These longitudinal studies have advanced our knowledge regarding this topic, but a number of limitations persist. In particular, most included only older women, and most of these subjects were White, and thus generalizability is limited.

Diet is an important source of inflammation.[21] The Dietary Inflammatory Index (DII) is a literature-derived dietary tool, which has been validated to assess the overall inflammatory potential of individual's diet.[21] Previous research has found that higher DII scores (indicating a more pro-inflammatory diet) are significantly associated with serum inflammatory markers (such as

C-reactive protein), suggesting a close relationship between this index and bio-humoral inflammatory parameters.[22] To the best of our knowledge, two studies have been conducted to examine the relationship of DII scores and fractures. One conducted in a large sample of American women reported finding that high DII scores, indicating a more inflammatory diet, was associated with increased hip fracture risk, although this finding was limited only to White women.[23] Another, more recent, case-control study in China, substantially confirmed these findings, in both genders.[24] However, it is unclear if a more pro-inflammatory diet is associated with fractures in men because only the Chinese included both sexes.[24] Knowing about a difference by sex could be important for tailoring intervention messages related to modulating diet to reduce inflammation.

Given this background, the purpose of this study was to investigate whether pro-inflammatory diets, as measured by the DII scores, are associated with increased incidence of fractures, using the data from a large cohort of North American adults. An important goal in using this cohort is to identify potential sex differences in the association between DII and fractures.

MATERIALS AND METHODS

Data source and subjects

Data were included from the Osteoarthritis Initiative (OAI) database. The OAI is freely available (<http://www.oai.ucsf.edu/>). Within the OAI, potential participants were recruited across four clinical sites in the United States of America (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. In this database, people were included if they: (1) had knee OA with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA[25] with data collected during baseline and screening evaluations in November 2008.

All participants provided informed written consent. The OAI study was given full ethical approval by the institutional review board of the OAI Coordinating Center of the University of California at San Francisco.

Dietary data and Dietary inflammatory index (exposure)

Dietary intake was assessed using a validated tool, the Block Brief 2000 Food Frequency Questionnaire (FFQ) during the baseline visit.[26] Seventy items were assessed to determine an individual's typical food and beverage consumption over the past year. The frequency of consumption was reported at nine levels of intake from "never" to "every day". In addition, seven dietary behavior questions were asked regarding food preparation methods and fat intake, one question on fiber intake, and 13 questions on vitamin and mineral intakes.

The details of the development of DII are extensively described elsewhere. [21] Briefly, in this updated version of the DII, 1943 articles were reviewed and scored. Forty-five food parameters, including foods, nutrients, and other bioactive compounds, were identified based on their inflammatory effect on six specific inflammatory markers, including CRP, IL-1 β , IL-4, IL-6, IL-10

and tumor necrosis factor (TNF)- α . A regionally representative world database representing diet surveys from 11 countries was used as a comparative standard for each of the 45 parameters (i.e. foods, nutrients, and other food components). Intake values from this database were used to calculate the DII scores. This is explained in more detail in the DII Methods paper.[21] Briefly, a standard mean for each parameter from the representative world database was subtracted from the actual individual exposure and divided by its standard deviation to generate Z scores. These Z scores were converted to proportions (thus minimizing effects of outliers/right-skewing). These values were then doubled and 1 was subtracted to achieve symmetrical distribution with values centered on 0. The resulting value was then multiplied by the corresponding inflammatory score for each food parameter and summed across all food parameters, to obtain the overall DII score. To assess construct validity, in a longitudinal cohort of ~600 subjects followed for a year multiple DII scores derived from up to 15 24-hour dietary recall interviews and up to five 7-day dietary recalls were related to up to 5 high sensitivity(hs)-CRP measurements taken over a year. It was found that the DII predicted interval changes in hs-CRP, and that the structured assessment (7-day dietary recalls) performed as well as the multiple 24HR-derived DII scores.[27] The DII was subsequently validated in four studies among different populations with a variety of inflammatory biomarkers (i.e. interleukin, IL-6, hs-CRP, fibrinogen, homocysteine and TNF- α).[22, 28-31]

For this study, from the FFQ we calculated the DII based on energy-adjusted intake of the 24 single food parameters of the 45 possible food parameters that were available from the FFQ using the energy density approach, which calculated the DII per 4184 kJ (1000 kcal) of energy.[32] The 24 food parameters available for DII calculation in this study were vitamin B₁₂, vitamin B₆, β -carotene, carbohydrate, cholesterol, fat, fiber, folic acid, iron, magnesium, monounsaturated fat acids (MUFA), niacin, protein, polyunsaturated fatty acids (PUFA), riboflavin, saturated fat acids (SFA), selenium, thiamin, vitamin A, vitamin C, vitamin E, vitamin D, zinc, niacin, and caffeine.

Outcome

The presence of fractures at baseline and during follow-up was obtained through self-reported history of fractures at the most common sites for osteoporosis, i.e. hip, spine and forearm.[33] Information regarding fractures were collected at V01 (1 year after baseline), V03 (2 years), V05 (3 years), V06 (4 years), V08 (6 years), and V10 (8 years).

Covariates

A number of variables was identified to explore the relationship between DII and incident fractures. These included: (1) race was defined as “Whites” vs. others; (2) smoking habits as “previous/current” vs. never; (3) educational level was categorized as “college” vs. others; (4) yearly income as $<$ or \geq \$50,000 and missing data; (5) body mass index (BMI), measured by a trained nurse; (6) co-morbidities assessed through the modified Charlson comorbidity score, with higher scores indicating an increased severity of conditions[34]; (7) daily intake of vitamin D, calcium, potassium (from food and from supplements), proteins and total energy intake; and (8) physical activity, evaluated using the Physical Activity Scale for the Elderly (PASE), a validated scale for assessing physical activity level in the elderly. The scale covers 12 different activities including: walking, sports and housework, and is scored from 0 upwards, without a maximum score.[35] Moreover, data regarding the use of drugs affecting positively bone metabolism (teriparatide, bisphosphonates, hormones) were also recorded.

Statistical analyses

Because the interaction between DII and sex in predicting fracture onset at follow-up was significant (p-value for interaction <0.0001) and the mean DII significantly differed between men and women (p <0.0001), all the analyses were stratified by sex.

All continuous variables were normally distributed according to the Kolmogorov-Smirnov test. Data were presented as means and standard deviation values (SD) for quantitative measures, and frequency and percentages for all discrete variables. Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch's ANOVA was used. P-values were calculated using the Jonckheere-Terpstra test[36] for continuous variables and the Mantel-Haenszel Chi-square test for categorical variables.

To assess the relationship between the DII score and incident fractures, a Cox's regression analysis was conducted where incident fracture was defined as the discrete "outcome", time-to-event was the temporal factor, and the DII score at baseline was the "exposure". The proportional hazards assumption was checked by plotting the Schoenfeld residuals versus time and it was confirmed that there were no violations in the assumption in any of the models. People who died during follow-up were censored on their date of death. The fully adjusted model included the following covariates: age (as continuous); total energy intake (in Kcal, as continuous); race (White vs. others); BMI (as continuous); education (college vs. others); smoking habits (current vs. previous/never); yearly income (> vs. <50,000 \$); Charlson co-morbidity index; use of drugs positively affecting bone metabolism (bisphosphonates, hormones); and physical activity scale for the elderly (as continuous). Only two people used teriparatide. Thus, this factor was not included as a potential confounder in the fully-adjusted model. Nutritional parameters (such as vitamin D, calcium, protein and potassium intakes) were not included in the fully adjusted model, since these estimates were already included in compute the DII score.

Multi-collinearity among covariates was assessed through variance inflation factor (VIF) [37], taking a cut-off of 2 as the criterion for exclusion. No covariates met this criterion and therefore none was excluded for this reason. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated to estimate the strength of the associations between DII score (reported in quintiles)

1 and incident fractures. P values for trend were calculated across DII groups using the Wald test,
2 based on a score derived from the median value of each DII group. We also used standardized
3 values of DII as a continuous exposure variable in some analyses.
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9 A $p < 0.05$ was deemed statistically significant. All analyses were performed using SPSS® software
10 version 21.0 for Windows (SPSS Inc., Chicago, Illinois).
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RESULTS

Sample selection

The OAI dataset initially included a total of 4,796 individuals. For 243 participants, there were insufficient data to calculate the DII score or an unreliable caloric intake was recorded (<500 or >5000 Kcal/day). At baseline, 788 participants had experienced a fracture and were excluded from the analysis. Finally, data from another 117 participants who were lost during follow-up (no sufficient data regarding fractures) also were excluded. Accordingly, 3,648 participants were included in analyses.

Descriptive characteristics

The cohort consisted of 1,577 males and 2,071 females. Mean age was 60.6 years (\pm SD 9.1 years; range: 45-79 years) and mean DII was -3.16 (\pm SD 1.68 points; range: -5.65 to 3.70). The mean DII was significantly higher in men than in women (2.82 ± 1.76 vs. 3.43 ± 1.57 , $p < 0.0001$).

Tables 1 (men) and **Table 2** (women) illustrate the baseline characteristics by DII quintiles. Independent of gender, participants with higher DII levels were significantly younger, consumed more calories and proteins, but less potassium, than those with lower DII values (p for trend < 0.0001 for all comparisons). Women with higher DII levels had less consumption of calcium and vitamin D (p for trend < 0.0001 for both comparisons) (**Table 1**). Regarding demographic characteristics, in both sexes, people with higher DII values were more frequently obese (p for trend < 0.0001), non-white (p for trend = 0.001) and less educated (p for trend < 0.0001). In women, people with higher DII levels were also poorer than those with lower DII values (p for trend = 0.01) (**Table 1**). Finally, in both sexes, people with higher DII levels took less frequently bisphosphonates (**Table 1**), although no significant differences emerged in terms of comorbidities.

Dietary inflammatory index and incident fractures

Over a mean follow-up of 8 years, 560 individuals (198 men and 362 women; =15.4% of the baseline population) developed a fracture for a global incidence of 24 (95%CI: 22-26) events for 1,000 persons-year.

As shown in **Table 3**, the incidence of fractures significantly increased with increasing DII scores (indicating higher pro-inflammatory diet) in women (Cox's regression analysis, $p < 0.0001$, **Figure 1**), but not in men ($p = 0.82$). Cox's regression analysis, adjusting for 10 potential confounders at baseline, with the lowest DII as reference (=Q1), showed that women with the highest DII score (=Q5) had a significantly higher risk for incident fracture (HR: 1.46; 95% CI: 1.02-2.11; $p = 0.04$; **Table 3**). This finding was not significant in men (Q5: HR=0.91; 95%CI: 0.54-1.54; $p = 0.73$) or in the sample as whole (Q5: HR=1.22; 95%CI: 0.91-1.64; $p = 0.19$).

An increase in one SD of DII (=1.68 points) increased the risk of fracture at follow-up in women (adjusted HR=1.14; 95%CI: 1.02-1.27; $p = 0.02$), but not in men (adjusted HR=0.95; 95%CI: 0.82-1.11; $p = 0.54$). However, the p for trend did not reach the statistical significance in either gender (p for trend=0.40 in men; p for trend=0.13 in women) (data shown only in text).

DISCUSSION

In this longitudinal study, we found that a more pro-inflammatory diet, as indicated by higher DII scores, were associated with higher incidence of fractures in women. During a follow-up period of 8 years, after adjusting for several potential confounders at baseline, women with the highest DII score (i.e. having a more pro-inflammatory diet) had a 46% higher risk of fracture. These findings, however, were not significant in men, suggesting important sex differences.

At baseline, women having higher DII values were significantly younger than those having lower values, but they experienced a higher risk of fractures in agreement with another study regarding the same topic. [23] In this regard, our study found similar results with another large cohort study conducted among American people which did not finding any significant associations between serum markers of inflammation (such as CRP and IL-6SR) and incident fractures.[18] The findings that higher DII values at baseline significantly predicted fractures in women are in agreement with one study on DII and incident fractures made in a large cohort of American women,[23] but not with another case-control study conducted in China, which found an association between DII score and hip fracture in both sexes.[24] However, it might be difficult to directly compare the findings of a case-control study to those of a longitudinal study, since it is hard to estimate the population risk from the case-control design versus the cohort design. We can offer some hypotheses to explain these findings. First, a methodological reason; because women were more well represented than men in the OAI study, it is possible that in men the association was not significant due to a lack of power. However, it should be noted that in the sample as whole the association between DII and incident fractures was not significant suggesting that physiopathological reasons are probably more important. Second, other studies reported that inflammation has different roles and mechanisms between men and women (e.g. for cardiovascular diseases)[38]; so, it is possible that for fractures the effect of inflammation is more evident in women than in men. More studies are needed because one large cohort study reported that higher serum CRP levels are associated with a higher fracture

1 risk in both men and women. [39] However, other large cohort studies found that the association
2 between inflammation and fractures is stronger in women than in men indirectly confirming our
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4 results.[18-20]
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9 Our findings substantially confirmed those already present in literature that suggest that higher
10 serum inflammation levels can lead to higher fracture rate.[15-17, 40] Inflammation can reduce
11 bone mass density through several mechanisms.[41] It has been reported that some pro-
12 inflammatory cytokines might play potential critical roles in the pathogenesis of perimenopausal
13 and late-life osteoporosis.[42] Several inflammatory cytokines seem to be involved in this process,
14 including C reactive protein, tumor necrosis alpha, IL 1 and IL6.[41] Briefly, it was reported that
15 the pro-inflammatory cytokines can lead to an over-activation of osteoclasts and to a reduction of
16 osteoblasts activity. [41]
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31 We believe that our findings might have important clinical consequences given the trend toward
32 more pro-inflammatory dietary patterns (i.e. diets rich in refined foods, sugars, flour or starch such
33 as diet typical of North American people) is increasing[43] and in women, in which both
34 osteoporosis and fractures are more common than in men, can have more deleterious effects on
35 bone metabolism. In this sense, other studies showed that healthy dietary patterns (such as
36 Mediterranean diet) are associated with a lower risk of fracture, particularly at hip [44-47] and it is
37 conceivable that these patterns have a reduced inflammatory power. DII is linearly associated with
38 serum markers of inflammation[22, 27-31], and consequently the possibility of modulating
39 inflammation with a healthier diet might provide important benefits to protect against fractures.
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41 Thus, encouraging people (particularly women) to eat healthier to prevent fractures can be of public
42 health importance.
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1 The findings of our research should be considered within its limitations. The principal shortcoming
2 is that we used self-reported information for adjudicating fractures and this can underestimate the
3 incidence of some osteoporotic fractures, such as vertebral ones.[48] Second, the comorbid medical
4 conditions assessed in this study were self-reported, introducing a possible recall bias. Another
5 limitation could be the non-availability of data on the remaining 21 food parameters of the DII.
6 Some components (such as turmeric, saffron and eugenol) are not consumed in high quantity in this
7 population, so non-availability of these food parameters may not have played major role in
8 association. However, inclusion of parameters such as flavonoids, which are commonly consumed,
9 may influence the results. Finally, the findings derived from the OAI include people with knee OA
10 or at higher risk of knee OA; therefore, they may not be fully generalizable to other populations.
11 Despite these limitations, this study is one of the few including both sexes and including not only
12 White participants.
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31 In conclusion, higher DII scores were associated with a higher incidence of fractures, even after
32 considering several potentially important confounders measured at baseline, only in women. Future
33 randomized controlled trials with diets rich in anti-inflammatory components are, however, needed
34 to confirm establish causality and consider if such interventions can reduce the incidence of
35 fractures.
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Conflict of interest: Dr. JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. NS is an employee of CHI. Prof. Reginster received consulting fees or paid advisory boards from IBSA-GENEVRIER, MYLAN, RADIUS HEALTH, PIERRE FABRE; lecture fees when speaking at the invitation of sponsor: IBSA-GENEVRIER, MYLAN, CNIEL, DAIRY RESEARCH COUNCIL (DRC) and grant supports from IBSA-GENEVRIER, MYLAN, CNIEL, RADIUS HEALTH.

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FIGURE LEGEND

Figure 1. Risk of fractures in women by dietary inflammatory index quintiles at baseline, Osteoarthritis Initiative (OAI), 2004-6.

Figure legend: Q1 indicates participants having the lowest dietary inflammatory index values; Q5 the highest. P values shown are for trends and were calculated using the Jonckheere-Terpstra test for continuous variables.

Table 1. Participants’ characteristics by dietary inflammatory index quintiles in men, Osteoarthritis Initiative (OAI), 2004-6.

	Q1	Q2	Q3	Q4	Q5	P
	(n=218)	(n=260)	(n=304)	(n=385)	(n=410)	value*
Age (years)	63.5 (9.1)	62.1 (9.3)	61.6 (9.5)	59.9 (9.4)	58.0 (9.3)	<0.0001
<i>Nutritional parameters</i>						
Energy intake (Kcal/day)	1355 (499)	1522 (572)	1491 (515)	1648 (622)	1758 (708)	<0.0001
Protein intake (g/day)	58.3 (24.6)	66.9 (29.0)	63.4 (23.8)	69.6 (29.1)	39.6 (30.8)	<0.0001
Calcium intake (mg/day)	700 (362)	752 (366)	681 (318)	713 (350)	682 (343)	0.41
Potassium (mg/day)	2872 (1138)	2868 (1159)	2568 (935)	2547 (1045)	2420 (1028)	<0.0001
Vitamin D intake (mg/day)	536 (202)	460 (221)	385 (214)	377 (240)	188 (163)	<0.0001
Alcohol intake (% of Kcal/day)	5.9 (6.6)	5.9 (7.2)	5.4 (7.1)	6.1 (7.5)	7.0 (9.0)	0.06
BMI (Kg/m ²)	27.3 (6.7)	28.2 (3.8)	28.8 (4.2)	29.3 (3.9)	29.5 (4.3)	<0.0001
<i>Demographics</i>						
White race (n, %)	188 (88.6)	228 (87.7)	260 (85.5)	328 (85.2)	323 (79.0)	0.003
Smoking (previous/current, n%)	111 (51.4)	137 (52.9)	150 (49.7)	206 (53.8)	197 (48.4)	0.52
College (n, %)	97 (44.5)	113 (43.5)	112 (36.8)	130 (33.8)	126 (30.9)	<0.0001
Yearly income (<50,000 \$, n, %)	154 (70.6)	194 (74.6)	219 (72.0)	269 (69.9)	274 (66.8)	0.27

	Q1	Q2	Q3	Q4	Q5	P
	(n=218)	(n=260)	(n=304)	(n=385)	(n=410)	value*
PASE (points)	178.4 (89.1)	188.5 (91.3)	172.4 (92.5)	177.5 (85.0)	173.6 (81.2)	0.21
<i>Medical conditions and medications</i>						
Charlson co-morbidity score	0.5 (1.1)	0.5 (1.0)	0.4 (0.8)	0.4 (0.9)	0.4 (0.8)	0.68
Hormones (n, %)	0 (0.0)	4 (1.6)	8 (2.6)	8 (2.1)	3 (0.7)	0.70
Bisphosphonates (n, %)	6 (2.8)	6 (2.3)	6 (2.0)	5 (1.3)	1 (0.2)	0.005

Abbreviations: BMI: body mass index; PASE: Physical Activity Scale for Elderly.

* P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical variables.

Data are means (with standard deviation) or number (and percentage) as appropriate.

Q1 indicates participants having the lowest dietary inflammatory index values; Q5 the highest.

Table 2. Participants’ characteristics by dietary inflammatory index quintiles in women, Osteoarthritis Initiative (OAI), 2004-6.

	Q1	Q2	Q3	Q4	Q5	P
	(n=512)	(n=470)	(n=425)	(n=345)	(n=319)	value*
Age (years)	62.4 (8.7)	61.8 (9.0)	60.2 (8.4)	60.0 (9.1)	57.3 (8.2)	<0.0001
<i>Nutritional parameters</i>						
Energy intake (Kcal/day)	1161 (394)	1263 (470)	1289 (481)	1329 (523)	1435 (636)	<0.0001
Protein intake (g/day)	52.8 (19.9)	57.4 (23.6)	57.0 (22.7)	56.4 (23.4)	55.8 (30.0)	0.02
Calcium intake (mg/day)	673 (346)	675 (331)	631 (303)	628 (307)	576 (331)	<0.0001
Potassium (mg/day)	2625 (996)	2522 (976)	2278 (860)	2169 (873)	1977 (980)	<0.0001
Vitamin D intake (mg/day)	582 (200)	490 (221)	436 (236)	349 (231)	167 (143)	<0.0001
Alcohol intake (% of Kcal/day)	3.0 (4.7)	3.4 (5.4)	4.0 (6.5)	4.2 (6.7)	3.6 (6.8)	0.03
BMI (Kg/m ²)	27.2 (4.8)	28.1 (4.8)	28.9 (5.4)	28.9 (5.4)	30.7 (5.8)	<0.0001
<i>Demographics</i>						
White race (n, %)	390 (76.3)	362 (77.0)	323 (76.0)	269 (78.0)	200 (62.7)	0.001
Smoking (previous/current, n%)	304 (59.7)	261 (55.8)	237 (56.2)	185 (53.8)	153 (48.1)	0.002
College (n, %)	160 (31.3)	121 (25.8)	111 (26.1)	76 (22.0)	54 (16.9)	<0.0001
Yearly income (<50,000 \$, n, %)	289 (56.4)	241 (51.3)	236 (55.5)	188 (54.5)	134 (42.0)	0.01

	Q1	Q2	Q3	Q4	Q5	P
	(n=512)	(n=470)	(n=425)	(n=345)	(n=319)	value*
PASE (points)	158.0 (76.7)	152.7 (75.8)	150.8 (78.0)	148.9 (73.6)	155.0 (82.5)	0.46
<i>Medical conditions and medications</i>						
Charlson co-morbidity score	0.3 (0.6)	0.4 (0.8)	0.4 (0.8)	0.4 (0.7)	0.4 (1.0)	0.17
Hormones (n, %)	8 (1.8)	9 (2.1)	11 (2.9)	5 (1.7)	4 (1.4)	0.78
Bisphosphonates (n, %)	108 (21.1)	90 (19.2)	71 (16.8)	55 (16.0)	26 (8.2)	<0.0001

Abbreviations: BMI: body mass index; PASE: Physical Activity Scale for Elderly.

* P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical variables.

Data are means (with standard deviation) or number (and percentage) as appropriate.

Q1 indicates participants having the lowest dietary inflammatory index values; Q5 the highest.

Table 3. Association between baseline dietary inflammatory index quintiles and incident fractures, Osteoarthritis Initiative (OAI), 2004-6.

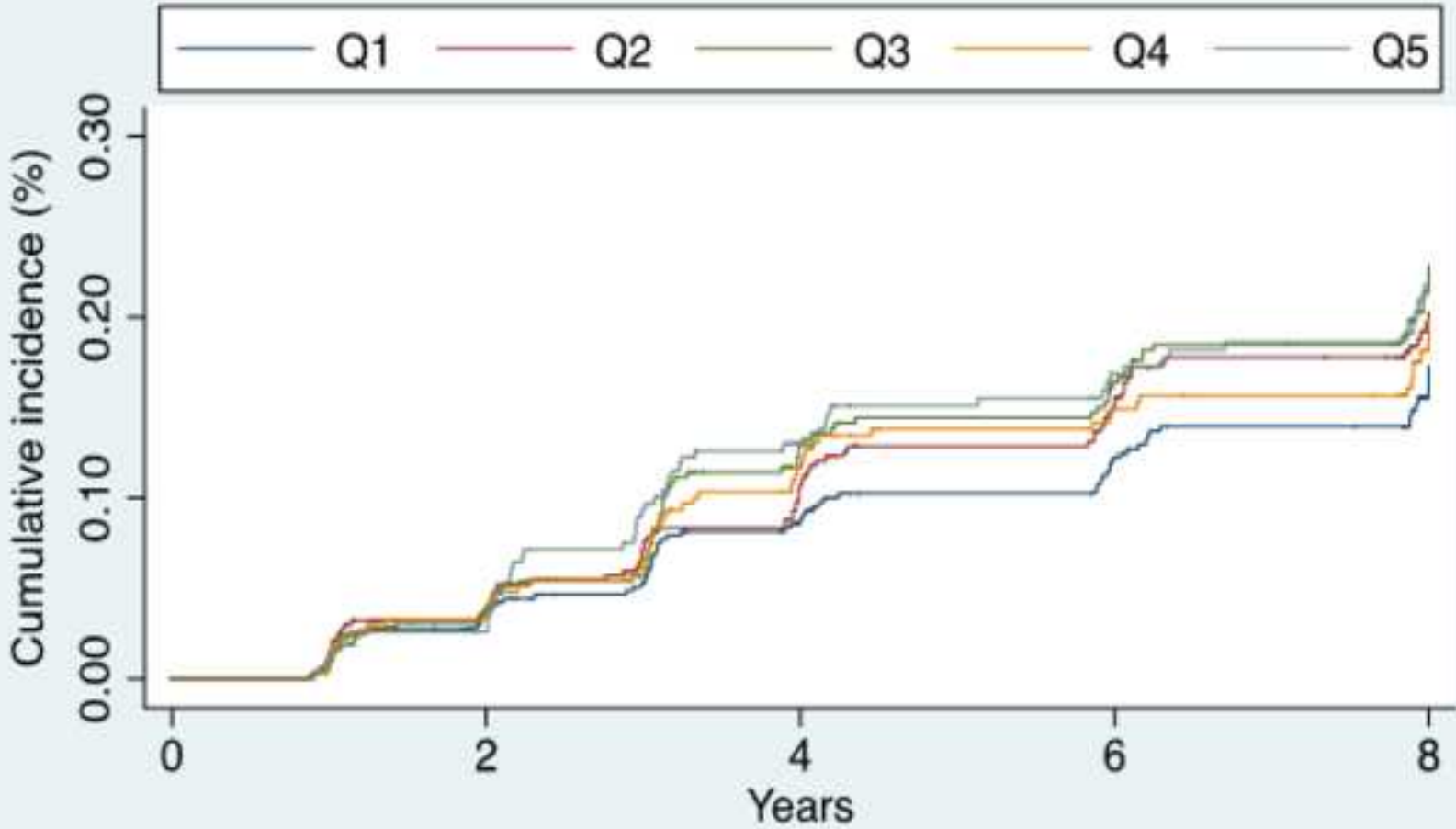
	Men				Women			
DII	Cases	Subjects	Incidence rate	HR* (95%CI) p-value	Cases	Subjects	Incidence rate	HR* (95%CI) p-value
Q1	25	218	17 (12-25)	1 [reference]	77	512	24 (19-29)	1 [reference]
Q2	39	280	23 (17-32)	1.21 (0.72-2.04) 0.47	81	470	28 (22-34)	1.11 (0.81-1.53) 0.47
Q3	45	304	24 (18-32)	1.29 (0.78-2.14) 0.33	86	425	32 (26-40)	1.42 (0.98-1.96) 0.07
Q4	44	385	18 (13-24)	0.91 (0.55-1.53) 0.73	59	345	27 (21-35)	1.26 (0.89-1.78) 0.20
Q5	45	410	18 (13-24)	0.91 (0.54-1.54) 0.73	59	319	32 (25-41)	1.46 (1.02-2.11) 0.04

Data are presented as hazard ratios (HRs) with correspondent 95% confidence intervals (CI).

Q1 indicates participants having the lowest dietary inflammatory index values; Q5 the highest.

* Fully adjusted hazard ratios included as covariates: age (as continuous); total energy intake (in Kcal, as continuous); race (white vs. others); body mass index (as continuous); education (college vs. others); smoking habits (current vs. previous/never); yearly income (> vs. <50,000 \$); Charlson co-morbidity index; use of drugs affecting positively bone metabolism (bisphosphonates, hormones); physical activity scale for the elderly (as continuous).

Women



Number at risk

Quintile = Q1	512	462	396	355	145
Quintile = Q2	470	429	355	314	138
Quintile = Q3	425	383	322	291	106
Quintile = Q4	345	310	260	229	94
Quintile = Q5	319	280	218	186	76

Introduction: A couple of key references are missing on line 44 that may inform your Discussion as well. Please add.

1. Cauley JA, Barbour KE, Harrison SL, Cloonan YK, Danielson ME, Ensrud KE, Fink HA, Orwoll ES, Boudreau R. Inflammatory Markers and the Risk of Hip and Vertebral Fractures in Men: the Osteoporotic Fractures in Men (MrOS). Journal of Bone Mineral Research. 2016 Dec;31(12):2129-2138
2. Ing SW, Orchard TS, Lu B, LaMonte MJ, Barbour KE, Cauley JA, Jackson RD. TNF Receptors Predict Hip Fracture Risk in the WHI Study and Fatty Acid Intake Does Not Modify this Association. J Clin Endocrinol Metab. 2015 Sep;100(9):3380-7.
3. Barbour KE, Boudreau R, Danielson ME, Youk AO, Wactawski-Wende J, Greep NC, LaCroix AC, Jackson RD, Wallace RB, Bauer DC, Allison MA, Cauley JA. Inflammatory Markers and the Risk of Hip Fracture: The Women's Health Initiative. Journal of Bone Mineral Research. 2012 May; 27 (5), 1167-1176

Reply: We thank the Reviewer for indicating us these relevant references that we have now added to our Introduction.

Methods: The Jonckheere-Terpstra test is a non-parametric trend test used when continuous variable does not meet parametric assumptions. This is not that clear why it was used. Looking at Tables 1 and 2 it does not appear that tests of trends were performed. Please clarify. <https://statistics.laerd.com/spss-tutorials/jonckheere-terpstra-test-using-spss-statistics.php>

Reply: We really thank the Reviewer for this appropriate comment and for the interesting link. However, according to the information given in this link, the Jonckheere-Terpstra test can be used also for continuous variables having a normal distribution. This test is similar to the Kruskal Wallis test only that there is an a priori ordering and has more statistical power. We finally confirmed that the p-values reported as footnotes in the tables are those given by the Jonckheere-Terpstra test.

For the Cox models, was the proportional hazards assumption tested? What about model fit?

Reply: Good point. We have added in the Statistical analysis that the proportional hazard assumption was checked by plotting the Schoenfeld residuals versus time and it was confirmed that the proportional hazard assumption was not violated in any of the regression models.

Results

Page 13. Lines 12-14. The interpretation of the p-value of Figure 1 appears to be that of a trend test; however that is not clear from the p-value reported <0.001. Was it a test of trend or difference? Please clarify.

Reply: Sorry for this inconvenience. The p-values reported are for trend as now declared.

Discussion: The second paragraph which attempts to explain the sex differences needs to cite the Cauley et al. that found an association in men. Also, for the second paragraph it needs to be acknowledged that it is difficult to compare the findings of a case-control study to those of a longitudinal study, as you cannot estimate the population risk from the case-control design versus the cohort (longitudinal) design. Finally, your argument for why this association is men but not women needs to be more developed and compelling. Need to update paragraph 3 with the studies listed above.

Reply: Thanks a lot for giving us the opportunity to expand our findings. In agreement with your request we have added these concepts in the Discussion section, as follows:

"At baseline, women having higher DII values were significantly younger than those having lower values, but they experienced a higher risk of fractures in agreement with another study regarding the same topic. [23] In this regard, our study found similar results with another large cohort study conducted

among American people which did not finding any significant associations between serum markers of inflammation (such as CRP and IL-6SR) and incident fractures.[18] The findings that higher DII values at baseline significantly predicted fractures in women are in agreement with one study on DII and incident fractures made in a large cohort of American women,[23] but not with another case-control study conducted in China, which found an association between DII score and hip fracture in both sexes.[24] However, it might be difficult to directly compare the findings of a case-control study to those of a longitudinal study, since it is hard to estimate the population risk from the case-control design versus the cohort design. We can offer some hypotheses to explain these findings. First, a methodological reason; because women were more well represented than men in the OAI study, it is possible that in men the association was not significant due to a lack of power. However, it should be noted that in the sample as whole the association between DII and incident fractures was not significant suggesting that physiopathological reasons are probably more important. Second, other studies reported that inflammation has different roles and mechanisms between men and women (e.g. for cardiovascular diseases)[38]; so, it is possible that for fractures the effect of inflammation is more evident in women than in men. More studies are needed because one large cohort study reported that higher serum CRP levels are associated with a higher fracture risk in both men and women. [39] However, other large cohort studies found that the association between inflammation and fractures is stronger in women than in men indirectly confirming our results.[18-20]”